FDA ODAC Meeting
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Gleevec Adjuvant GIST

Subpart H Phase IV Commitments

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Presentation Overview

- History of Gleevec approvals & commitments
- Approval history of Adjuvant GIST
  - ACOSOG Z9001 study
  - Summary results
- Gleevec Adjuvant GIST Subpart H commitments
  - ACOSOG Z9001 study
  - SSG XVIII/AIO study
  - Challenges in delivering commitments
- Summary

ACOSOG - American College of Surgeons Oncology Group
SSG - Scandinavian Sarcoma group
AIO - Arbeitsgemeinschaft Internistische Onkologie [Translation: Working Group of Medical Oncologists]

Gleevec Approved for 10 Indications

2001 **Patients with Ph+ CML in BC, AP, or CP after IFN failure**

2002 **Newly diagnosed adult patients with Ph + CML in CP**

2002 **Patient with Kit + unresectable and/or metastatic malignant GIST**

2006 **Pediatric patients with Ph+ CML in CP, newly diagnosed or recurred after SCT or resistant to IFN therapy**

2006 5 rare diseases in adult patients with

- Relapsed or refractory Ph+ ALL
- Myelodysplastic Syndrome (MDS)/ Myeloproliferative Disorders (MPD) associated with PDGFR gene rearrangements
- Aggressive Systemic Mastocytosis (ASM) without D816V c-Kit mutation or c-Kit mutational status unknown
- Hypereosinophilic Syndrome (HES)/ Chronic Eosinophilic Leukemia (CEL) who have FIP1L1-PDGFRα fusion kinase, kinase negative or unknown
- Unresectable, recurrent and/or metastatic Dematofibrosarcoma Protuberans (DFSP)

2008 **Adjuvant treatment of adult patients with Kit + GIST**

Gleevec FDA Commitment Background

- Gleevec is approved for **10 Indications**
  - Total of 33 commitments
- **5** Indications Regular approval
  - 6 Post-Marketing Commitments
    - 3 released, 3 remaining
- **5** Indications under Subpart H
  - 14 accelerated approval
  - 13 Post-Marketing Commitments

Subpart H Approvals: Time to Full Approval

Indication	Subpart H Approval	Full Approval	Commitments AA*	PMC	Fulfilled
Original CML	10 May 2001	8 Dec 2003	2	8	10
Newly Diagnosed CML	20 Dec 2002	27 May 2009 (6 yearly updates)	1	1	2
Pediatric CML: a) Original **b) Newly Diagnosed**	 20 May 2003 27 Sept 2006	 13 June 2006 2 Apr 2011-Action Date	 1 1	 0 0	 1
Metastatic GIST	1 Feb 2002	26 Sept 2008	5	4	9
Adjuvant GIST	19 Dec 2008	Ongoing	4	0	

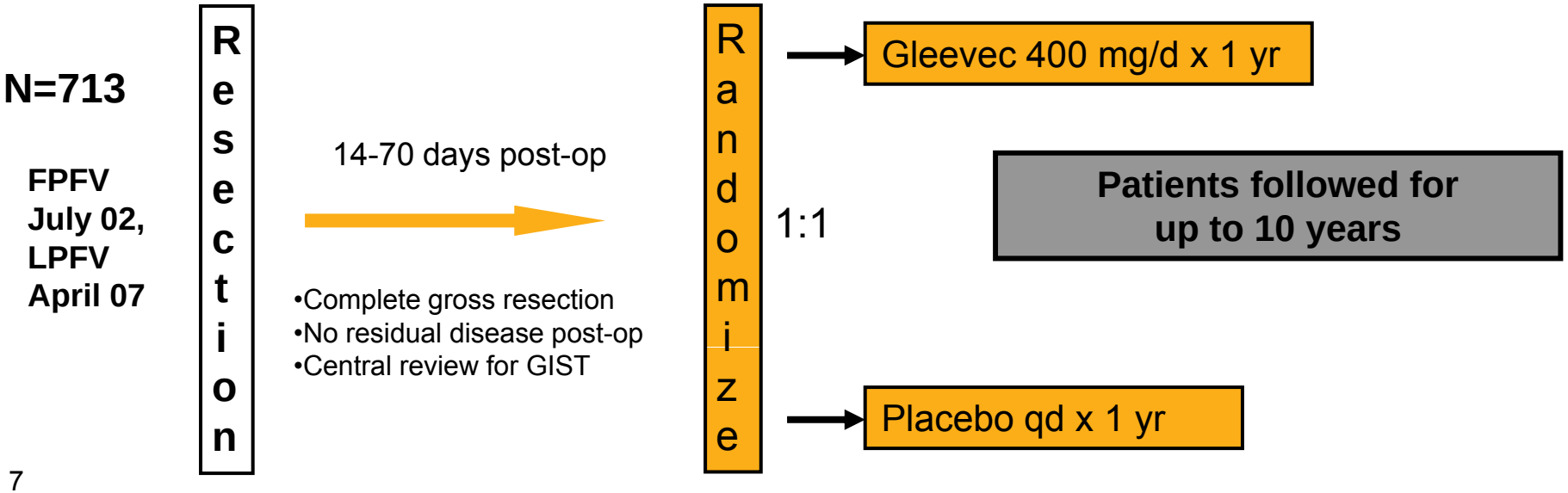
* Subpart H Accelerated Approval

Gastrointestinal Stromal Tumor (GIST) Background

- GISTs are mesenchymal neoplasms of the GI tract
- 10–20 cases/million diagnosed in the US annually
- Surgery is standard treatment for local disease
- Recurrence of GIST following surgery is common
  - Median time to recurrence is 2 years
- Median OS in advanced GIST;
  - ~10 months prior to Gleevec availability
  - ~5 years with Gleevec

Adjuvant GIST ACOSOG Z9001 Pivotal Study

- Study conducted by ACOSOG under a CRADA (NCI & Novartis)
  - In collaboration with NCIC, CALGB and SWOG
- GIST expressing KIT (CD117), tumor ≥3cm, no post-operative chemotherapy /radiation therapy
- Primary endpoint: recurrence free survival (RFS)
- Secondary endpoint: overall survival (OS)



Study Z9001: Results of Key Analyses Leading to Approval

- Efficacy
  - Primary endpoint: Gleevec prolonged RFS vs. placebo:
    - HR=0.398; 95% CI 0.259-0.610; (p<0.0001)
  - 14 month median follow-up;
    - 30 RFS events Gleevec vs 70 RFS events placebo
  - OS endpoint: no significance (only 13 events observed)
- Safety
  - Well tolerated with no unexpected/new AEs reported

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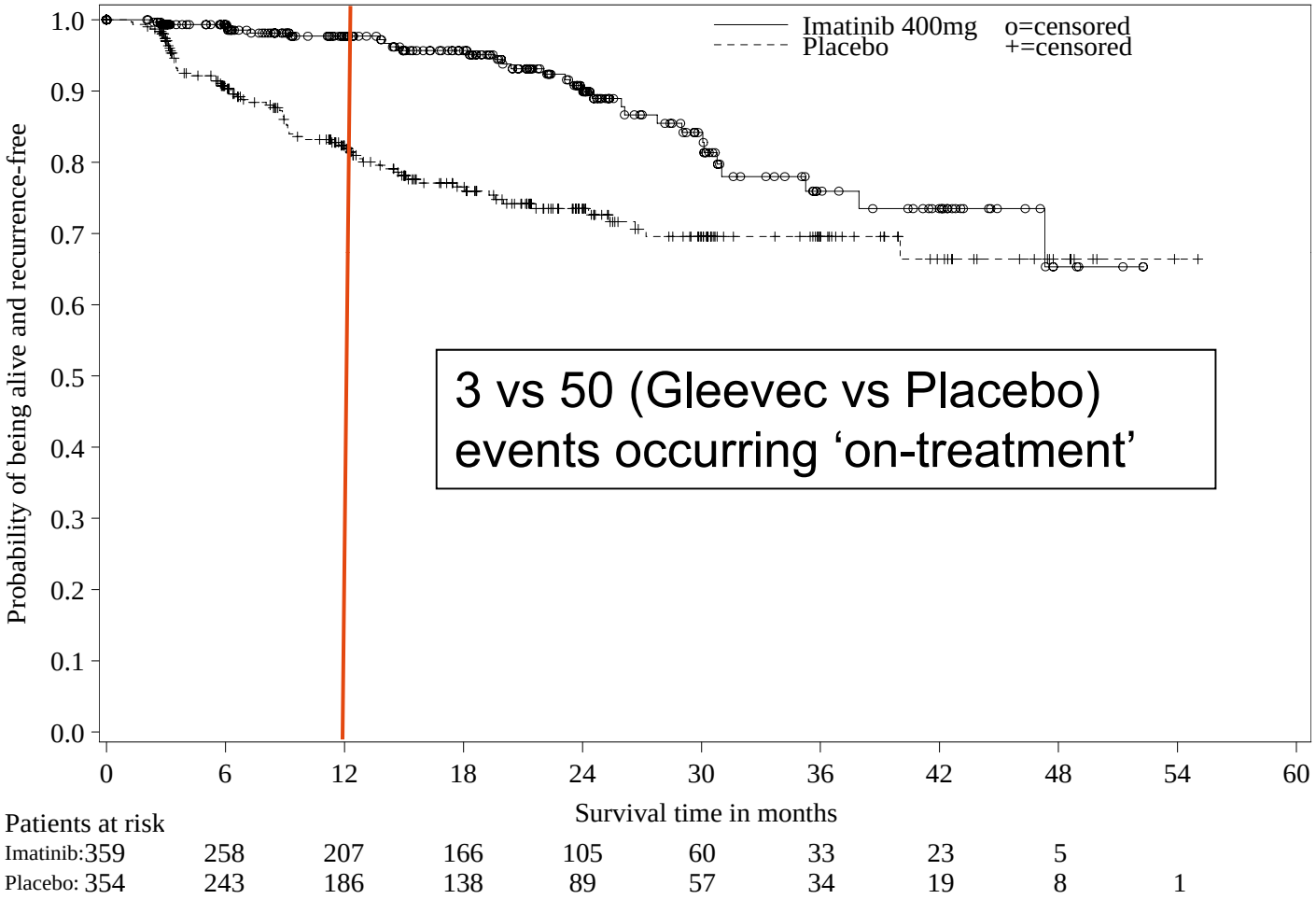
Kaplan-Meier Estimate of Recurrence-Free Survival (Final ITT Population)



Subpart H Commitments

- **FDA request: Follow-up data on ACOSOG Z9001 (survival and rate of recurrence)**
- Agreement: Provide ACOSOG Z9001 data as requested

- **FDA request: Initiate study to assess optimal length of adjuvant Gleevec treatment (e.g. 1 year vs. 2 year treatment)**
- Novartis Proposed: Ongoing Scandinavian Sarcoma Group trial SSG XVIII/AIO, comparing 12 vs. 36 month adjuvant Gleevec treatment in a randomized, prospective phase III study
- Agreement reached

Study ACOSOG Z9001

Z9001 Collaboration for FDA Submission (1/2)

- Novartis provided ongoing support & collaboration from study inception
- FDA meeting EOP 2 meeting April 2003
  - Agreement reached on primary registration endpoint, RFS
- Significant treatment effect seen at early interim analysis
- Trial results announced via NCI alert April 2007
- Novartis immediately began to prepare for HA submission in collaboration with:
  - ACOSOG
  - Mayo Clinic - statistical unit of ACOSOG, input to analysis plan
  - Duke Clinical Research Institute (DCRI): project coordination, in-house monitoring , statistics & data management

Z9001 Collaboration for FDA Submission (2/2)

- Key activities undertaken included:
  - Collection of outstanding data
  - Implementation of independent blinded review
  - Cleaning database
  - Coding of AEs
  - Statistical Analysis Plan
  - Novartis ensured data quality requirements were met
- FDA submission June 2008
- FDA approval December 2008

Z9001 Collaboration for Post Approval Commitments- Activities

- Immediately following approval, Novartis began working with ACOSOG to fulfill PACs
- ACOSOG directed Novartis to work with Mayo; DCRI no longer involved
- Scope of work to meet commitments fully defined and agreed in April 2009
- Three contract amendments executed between ACOSOG and Novartis during 2010
- Contract between ACOSOG and Mayo executed late 2010
- Mayo currently working to clean and complete database in preparation for statistical outputs

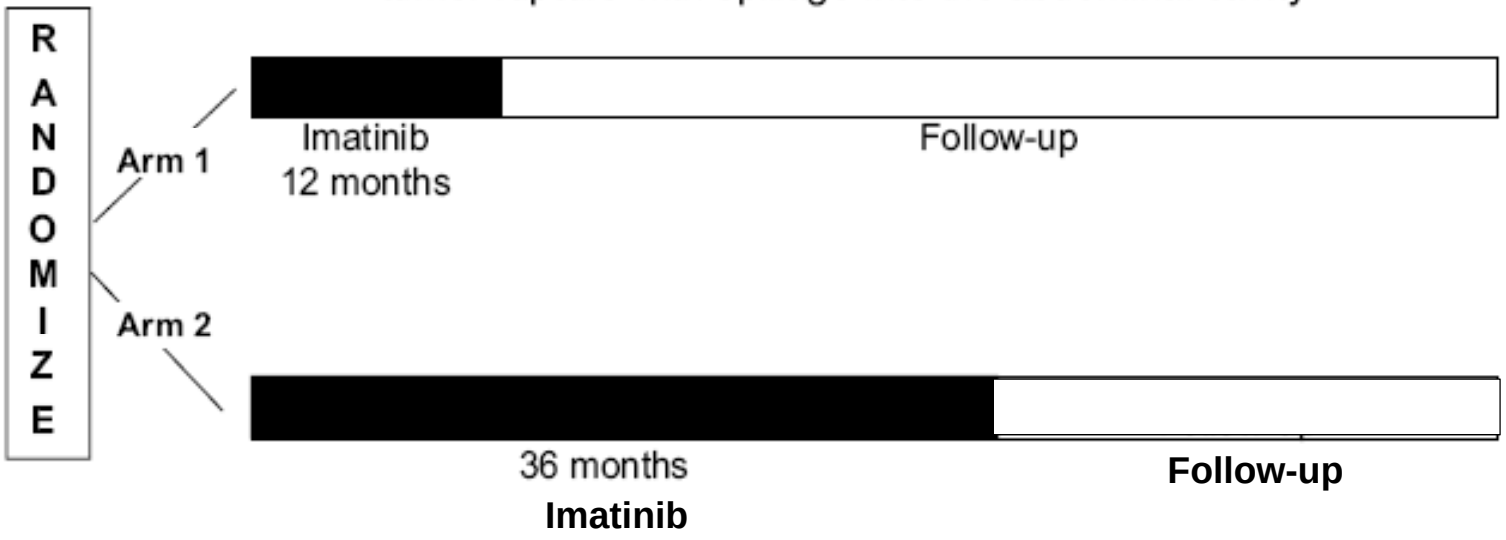
Z9001 Collaboration for Post Approval Commitments- Challenges

- Need for multiple contracts and amendments with several legal entities
- Execution of terms of complex contracts
  - For example: timely transfer of funds between third parties
- Competing priorities of third parties

Study SSG XVIII/AIO

SSG XVIII/AIO Study Background

Open label, multicenter phase III study for
High risk GIST
- >10 cm
- >10 mit/50 HPF
- >5 cm and >5 mit/50 HPF
- tumor rupture with spillage into the abdominal cavity



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•FPFV Feb 2004
•LPFV Sept 2008

SSG XVIII/AIO Study Background

Short (12 months) versus long (36 months) duration of adjuvant treatment with the tyrosine kinase inhibitor imatinib mesylate of operable GIST with a high risk of recurrence

- Primary endpoint: RFS
- Secondary endpoint: OS
- Final analysis: All randomized patients (n=400) complete 1st visit following 1 yr treatment & at least 110 events
- Follow-up OS analysis: 5 years after final analysis

SSG XVIII/AIO Study Background

- Novartis has been working collaboratively with SSG
  - Statistical analysis plan finalized
  - Data collection and monitoring prospectively supported
  - Novartis will ensure data quality requirements will be met
- Data cutoff: Final analysis December 31, 2010
- Database prepared by SSG
- Data collection being completed, data cleaning ongoing

Subpart H Adjuvant GIST Commitments

Agreed Post Approval Commitments (PACs)

Commitment	Description	Due	Comments
1	ACOSOG Z9001 4-year follow-up study report & datasets for RFS	30 Nov 2010	Delayed Novartis will provide Clinical Study Report (CSR) within 10 weeks of final data receipt
2 & 3	ACOSOG Z9001 5-year follow-up study report & datasets for RFS and OS	30 Nov 2011	Actively working to meet commitment
4	SSG XVIII/AIO final study report & datasets	30 Nov 2011	Actively working to meet commitment

Summary

- Novartis has already fulfilled 25 Post-marketing and Subpart H commitments for Gleevec
- We are working actively to deliver on all remaining commitments
- Novartis is working diligently to influence/address complexities encountered in working with cooperative groups for regulatory filings.